Work-up/Follow-up: Baseline and Surveillance Studies for Cutaneous Melanoma Patients

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Key Aspects of Workup following Melanoma Diagnosis

**History - including focused review of systems:**
- Constitutional, neurologic, respiratory, hepatic, gastrointestinal, musculoskeletal, skin, lymphatics
- Pay attention to unanticipated weight loss, general malaise, profound fatigue, headaches or other CNS symptoms

**Physical Examination:**
- Total body skin examination
- Palpation of lymph nodes (regional and distant)
- Consider abdominal exam
  - large tumors with satellite, in-transit, or regional nodal metastasis at presentation
  - uveal melanoma
Additional Studies for Workup of the Newly-diagnosed Melanoma Patient

Why do it?

- Assess the extent of disease
- Establish baseline images for future comparison (in patients at risk for relapse)
- Detect clinically occult disease which may affect treatment recommendations
- Define homogeneously-staged patients for clinical trials
Why not perform baseline workup?

- **NO GOOD DATA TO SUPPORT IN ASYMPTOMATIC PTS**
  - No prospective, randomized trials
  - Most evidence based on retrospective data

- **Current tests have relatively insensitive lower limits of resolution**

- **Cost** associated with obtaining baseline studies **high**

- **False positive** results associated with:
  - increased **patient anxiety**
  - increased **morbidity** with more invasive tests
Screening Bloodwork

- Hematologic tests lack both high sensitivity and high specificity for melanoma detection
- LDH – independent predictor of survival - stage IV only
- What about cutaneous melanoma patients?
  - 224 patients with CM; screening LDH in 96
  - 15% (14/96) had elevated LDH at baseline
  - Did not lead to detection of systemic disease, alter surgical management, or correlate with SLN postivity
- Serum S-100B
  - Further study necessary to assess utility in routine staging
  - At present, limited to advanced disease

Baseline Imaging Studies: Chest X-ray

- Multiple studies (retro- and prospective) have found consistent false-positive rates.
- True positive rate low: 0% to 0.5%.
- Despite availability and low cost, CXR is a highly cost inefficient test in asymptomatic patients with cutaneous melanoma.
- Routine use not justified at baseline.

Computed Tomography (CT)

- **Body CT** not useful for detection of occult metastasis in patients with primary melanoma.
- Most recent study 158 pts, T1b-T3b melanoma, clinically node negative (N0):
  - Chest CT – false positive (FP) rate 87.5%.
  - CT abdomen/pelvis - 90.9% FP rate.
  - 57 head CTs - 100% FP rate.
- **NO True Positive Findings!**
- **Conc:** minimal benefit for preoperative CT scans
  - Low yield, high FP rate, no change in surgical management/staging, assoc with additional (invasive) studies, increased patient anxiety.

Positron Emission Tomography (PET)

- More sensitive/specific than CT for melanoma staging, but more costly; usually integrated with CT

- Highest utility – DISTANT METASTASIS detection in the setting of documented/suspected metastasis (stage III, IV) or for surveillance of metastatic disease

- Positive scan may impact further surgery and/or need for systemic therapy

- Not a substitute for sentinel lymph node biopsy (SLNB) staging in primary melanoma patients

Who Should be Imaged at Baseline?
## Work-up of Primary Melanoma: NCCN Guidelines

<table>
<thead>
<tr>
<th>Stage</th>
<th>NCCN Recommended Workup</th>
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<tbody>
<tr>
<td><strong>Stage 0</strong> (in situ)</td>
<td>None</td>
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<tr>
<td><strong>Stage IA</strong></td>
<td>H&amp;P  &lt;br&gt; Routine imaging/labs not recommended  &lt;br&gt; Imaging only to evaluate specific signs or symptoms (CT scan, PET-CT, MRI)</td>
</tr>
<tr>
<td>≤1 mm thick, no ulceration, mitotic rate &lt;1/mm²</td>
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<tr>
<td><strong>Stage IB, Stage II</strong></td>
<td>H&amp;P  &lt;br&gt; Routine imaging/labs not recommended  &lt;br&gt; Imaging (CT scan, PET, MRI) only as clinically indicated  &lt;br&gt; <strong>SIMILAR TO AAD 2011 GUIDELINES!</strong></td>
</tr>
<tr>
<td>(≤1 mm thick with ulceration or mitotic rate ≥1/mm² or &gt;1 mm thick, any characteristic), N0</td>
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Baseline and Surveillance Studies (NCCN)

- For all **ASYMPTOMATIC** stage I and II Melanoma (including T4 lesions) at **BASELINE**:
  - LFTs, LDH, CXR, CT and/or PET-CT **NOT INDICATED**!

- Same true for **SURVEILLANCE**:
  - Routine blood tests not recommended
  - Radiologic imaging (CT, PET/CT, MRI) **only indicated to investigate specific signs or symptoms**
  - Screening for asymptomatic recurrent/metastatic disease in patients with Stage 0-IIA **NOT RECOMMENDED**; optional for Stage IIB-IV
  - Consider CXR, brain MRI, or PET-CT q3-12 months
  - No imaging for asymptomatic pts of **ANY STAGE** after 3-5 years!
Site and Timing of Melanoma Relapse

- **429 patients with** surgically-resected stage III melanoma, no evidence disease, 1992-2004

- **Overall 5-year relapse-free survival:**
  - Stage IIIA - 63%
  - Stage IIIB - 32%
  - Stage IIIC - 11%

- **Sites of 1st relapse:** local/ in-transit (28%), regional nodal (21%), systemic (51%)
  - Radiologic tests detected only 32% of relapses, most by pt or family

- **Routine physical exam unlikely to detect 1st relapse after**
  - 3 years for stage IIIA, 2 years for stage IIIB, and 1 year for stage IIIC
  - Same true for imaging beyond 3 years for stage IIIA/IIIB & 2 years for IIIC

Melanoma Surveillance

- Careful Hx and PE detect most metastases, **NOT surveillance studies**
  - Labs almost never sole indicator of metastatic disease; CXR rarely
  - LDH - staging value only for stage IV melanoma – **AT TIME OF DIAGNOSIS**

- Extensive radiologic scans (CT/ MRI/ PET/ skeletal survey) **generally not** of value in asymptomatic pts

- Presymptomatic detection of stage IV melanoma **does not affect survival** – **will this change with the newer drugs?**

Intensive Imaging for High-risk Melanoma

- Prospective study 290 pts with stage IIB, IIC, III melanoma
  - underwent intensive imaging and clinical surveillance

- 114 (39%) developed metastasis – MEDIAN 1.4 years
  - Imaging (CT C/A/P, brain MRI q 6 mos x 5 years) detected 67% metastasis (mostly distant)
  - Clinical exam (pt or provider) detected 49% (mostly skin, LNs)

- Limitations - NO assessment of:
  - patient outcomes (e.g. improved survival due to imaging detection)
  - cost-effectiveness
  - potential patient harms (adverse effects of false positive findings)

Common Follow-up Recommendations for All Patients

- At least annual skin exam for life

- Educate all patients in:
  - regular skin self-examination, lymph node self-exam for invasive disease

- **Surveillance regional nodal ultrasound** may be considered in patients:
  - with equivocal LN exam
  - who were offered but did not undergo SLNB
  - in whom SLNB not possible/successful
  - with a positive SLNB who did not undergo complete lymph node dissection (CLND)
  - Not a substitute for SLNB or CLND!

Role of Ultrasound (US) in Regional Nodal Basin Follow-up

- Prospective study (1288 pts) demonstrated higher sensitivity (89%) compared to clinical examination (71%)
  - Provided earlier diagnosis of in-transit and regional LN metastasis after initial surgery

- Meta-analysis: US superior to palpation for assessment of regional lymph node metastasis and surveillance of regional LN fields
  - When clinical findings equivocal and/or clinical suspicion is high

- Meta-analysis: 74 studies, 1990-2009, 10,528 patients
  - Ultrasonography superior to CT, PET, and PET-CT for detecting lymph node metastases
  - Increased Radiology adoption of ultrasound for this purpose nec in the US!

# Primary Melanoma Surveillance

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| **Stage 0 (in situ)**  | - At least annual skin exam for life (ALL PATIENTS)  
- Educate patient in regular self skin exam (ALL PATIENTS)                                                                                                                                     |
| **Stage IA-IIA NED**   | - H&P (with emphasis on nodes and skin) every 6-12 mo x 5 y, then annually as clinically indicated  
- At least annual skin exam for life  
- Educate patient in regular self skin and LN exam (stage IA-IV)  
- Routine blood tests/radiologic imaging to screen for asymptomatic recurrent/metastatic disease **not recommended**                                                                |
| **Stage IIB-IV NED**   | - H&P (emphasis on nodes and skin)  
  - Every 3-6 mo for 2 yr, then  
  - Every 3-12 mo for 3 yr, then annually as clinically indicated  
- Routine blood tests not recommended  
- Consider **CXR, CT, brain MRI, and/or PET-CT every 3-12 mos** to screen for recurrent/metastastic disease  **(category 2B)**  
- **Routine radiologic imaging not recommended after 3-5 y**                                                                                           |
AAD Guidelines 2011

● **Baseline:**
  – No baseline lab or imaging studies in asymptomatic patients with newly-diagnosed primary melanoma of any thickness

● **Surveillance:**
  – Surveillance labs/imaging studies have low yield for metastatic detection and high false-positive rates
  – Regular clinical follow-up and interval patient self exam of skin and regional LNs
  – History and PE findings direct need for further studies to detect metastatic disease
  – No clear f/u interval – at least annual history and PE with attention to skin and lymph nodes

What About Newer Molecular Techniques?

- “While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is **NOT RECOMMENDED** outside of a clinical study (trial).”
  - myPath®, Myriad Genetics, Inc.
  - DecisionDx®, Castle Biosciences, Inc.

- **Somatic mutational analysis (BRAF, NRAS, KIT)** recommended if patients are being considered for either routine treatment or clinical trials, but not in the absence of metastatic disease
  - “BRAF testing of the primary cutaneous melanoma is not recommended unless required to guide systemic therapy.”
Opinions vary regarding appropriate follow-up.

Follow-up schedule influenced by:
- Risk of disease recurrence and new primary melanoma
- Previous primary melanoma; h/o atypical nevi
- Family history
- Patient anxiety

Optimal duration of follow-up controversial
- Probably not cost effective to follow patients intensely after 5-10 years
- Lifetime dermatologic surveillance recommended due to risk of second primary melanoma (4-8%)
- Frequency of dermatologic surveillance based on individual risk factors
Conclusions

- Patient history and thorough physical examination are the key components of initial workup and surveillance in the melanoma patient.
- Following surgical resection, regular CLINICAL follow-up is the most important means of detecting local, regional and distant disease.
- Surveillance imaging recommendations may change as adjuvant therapies for lower stage disease evolve.
How to Access the NCCN Guidelines

● Go to: NCCN Clinical Practice Guidelines in Oncology – NCCN.org

● For Health Care Professionals:
  – www.nccn.org/professionals/physician_gls/

● Click on “NCCN Guidelines for Treatment of Cancer by Site”

● Then on “MELANOMA” - PDF File: “NCCN Guidelines”

● Register with email address and create account - FREE!